REMARKS

I. Request for Consideration of a Further Supplemental Information Disclosure Statement

Applicants respectfully request the Examiner's consideration of the further Supplemental IDS which accompanies this response and entry into the record.

II. Discussion of the Rejection under 35 U.S.C. Sec. 103(a) over Lundberg

Claims 1, 2, 4-7 and 13-21 stand rejected under 35 U.S.C. Sec. 103(a) as allegedly unpatentable over Lundberg (U.S. Patent No. 6,132,770). Applicants respectfully traverse the rejection.

Art which teaches effervescing tablets is non-analogous to the present invention; directed to tablets which rapidly dissolve buccally. Applicants have previously provided experimental evidence to prove the non-obviousness of the present invention. In response, the Examiner's comments on the Advisory Action state that the Declaration appeared "to confirm that the tablet of Lundberg would effervesce in the mouth".

Applicants submit that whether or not the Lundberg tablets are capable of effervescing in the mouth is irrelevant. The effervescence of the Lundberg tablets in the mouth does not make the Lundberg reference analogous art.

In attached Appendix A, a supplemental reference is provided for the Examiner's consideration. The supplemental reference is an excerpt from the European Pharmacopoeia, the portion which provides definitions of effervescent tablets and orodisperse tablets. There is no indication that effervescent tablets should or even can be placed directly into the mouth for administration in the definition of effervescent tablets. The supplemental reference confirms what one skilled in the art of formulation chemistry already recognizes and understands - that effervescent tablets are not designed to be placed directly into the mouth; as well as that references teaching effervescent tablets are non-analogous art for inventions directed to preparations for rapid buccal dissolution.

The Examiner has indicated in the Final Office Action dated July 21, 2004 that "the burden is shifted to applicant to submit data showing that the effervescent dosage form of Lundberg does not exhibit the buccal disintegration time being claimed" and also that "the burden is shifted to applicant to establish that the effervescent composition of Lundberg does not disintegrate in a patient's mouth."

Accompanying this response is a further Declaration which meets the Examiner's requirements. Note that in the results section on page 5 it is indicated that when Lundberg-type effervescent tablets were ingested by test subjects, they were spat out as intolerable after 3 minutes in the mouth. Yet even though the tablets had been in the mouth for three minutes, not even half of the tablet had disintegrated. Thus, Lundberg –type effervescent tablets do not dissolve buccally in the claimed time range.

Applicants have shown that tablets taught by the Lundberg reference do not dissolve buccally in 5-50 seconds. They have also attempted to show the Examiner that effervescent tablets are not designed for buccal administration, by illustrating that they cannot be tolerated by human patients. The experiments prove what is well-understood by those skilled in the art of formulation chemistry, that the cited art is simply non-analogous.

Independent claim 1 recites rapidly disintegrable solid preparations which are bucally dissolved in a specified amount of time. Tablets of the cited art are incapable of such dissolution, as Applicants have proven in the Declaration. The proof in the Declaration underlines the Applicants' position that the cited art is non-analogous. Therefore, the cited reference does not teach or suggest Applicants' invention as set forth in claim 1.

Claims 2, 4-7 and 13-17 depend upon claim 1. Applicants submit that the more specific dependent claims are also unobvious for the reason provided above.

Independent claim 21 is directed to tablets, while independent claims 18-20 are directed to methods. In each of these claims, a specific range of buccal dissolution time is recited. As explained in the preceding paragraphs, the cited art does not teach or suggest the methods or tablets which are buccally dissolved.

Therefore Applicants respectfully request withdrawal of the 35 U.S.C. Sec. 103(a) rejection over Lundberg.

III. Acknowledgement of the Allowable Claims

Applicants hereby acknowledge the Examiner's indication of the allowability of claims 9-11. However, Applicants respectfully request that the patentability of these claims be confirmed upon consideration of the further Supplemental Information Disclosure Statement discussed in Sec. I. above.

IV. Conclusion

Reconsideration and allowance of the claims is requested in light of the arguments provided above. Should the Examiner believe that a conference with Applicants' attorney would advance prosecution of this application, she is respectfully requested to call Applicants' attorney at (847) 383-3391.

Respectfully submitted,

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Appendix A

For tablets for which subdivision is authorised, it is demonstrated to the satisfaction of the competent authority that the subdivided parts comply either with test A for *Uniformity of content of single-dose preparations* (*2.9.6*) or with the test for *Uniformity of mass of single-dose preparations* (*2.9.5*), as appropriate.

In the manufacture, packaging, storage and distribution of tablets, suitable means are taken to ensure their microbiological quality; recommendations on this aspect are provided in the text on *Microbiological quality of pharmaceutical preparations* (*5.1.4*).

TESTS

Uniformity of content (*2.9.6*). Unless otherwise prescribed or justified and authorised, tablets with a content of active substance less than 2 mg or less than 2 per cent of the total mass comply with test A for uniformity of content of single-dose preparations. If the preparation has more than one active substance, the requirement applies only to those substances which correspond to the above conditions.

Unless otherwise justified and authorised, coated tablets other than film-coated tablets comply with test A for uniformity of content of single-dose preparations irrespective of their content of active substance(s).

Uniformity of mass (*2.9.5*). Uncoated tablets and, unless otherwise justified and authorised, film-coated tablets comply with the test for uniformity of mass of single-dose preparations. If the test for uniformity of content is prescribed or justified and authorised for all the active substances, the test for uniformity of mass is not required.

Dissolution. A suitable test may be carried out to demonstrate the appropriate release of the active substance(s), for example one of the tests described in *Dissolution test for solid dosage forms* (*2.9.3*).

Where a dissolution test is prescribed, a disintegration test may not be required.

Uncoated tablets

DEFINITION

Uncoated tablets include single-layer tablets resulting from a single compression of particles and multi-layer tablets consisting of concentric or parallel layers obtained by successive compression of particles of different composition. The excipients used are not specifically intended to modify the release of the active substance in the digestive fluids.

Uncoated tablets conform to the general definition of tablets. A broken section, when examined under a lens, shows either a relatively uniform texture (single-layer tablets) or a stratified texture (multi-layer tablets) but no signs of coating.

TESTS

Disintegration. Uncoated tablets comply with the test for disintegration of tablets and capsules (*2.9.1*). Use *water R* as the liquid. Add a disc to each tube. Operate the apparatus for 15 min, unless otherwise justified and authorised, and examine the state of the tablets. If the tablets fail to comply because of adherence to the discs, repeat the test on a further 6 tablets omitting the discs. The tablets comply with the test if all 6 have disintegrated.

Chewable tablets are not required to comply with the test.

Coated tablets

DEFINITION

Coated tablets are tablets covered with one or more layers of mixtures of various substances such as natural or synthetic resins, gums, gelatin, inactive and insoluble fillers, sugars, plasticisers, polyols, waxes, colouring matter authorised by the competent authority and sometimes flavouring substances and active substances. The substances used as coatings are usually applied as a solution or suspension in conditions in which evaporation of the vehicle occurs. When the coating is a very thin polymeric coating, the tablets are known as film-coated tablets.

Coated tablets have a smooth surface which is often coloured and may be polished; a broken section, when examined under a lens, shows a core surrounded by one or more continuous layers with a different texture.

PRODUCTION

Where justified, uniformity of mass or uniformity of content of coated tablets other than film-coated tablets may be ensured by control of the cores.

TESTS

Disintegration. Coated tablets other than film-coated tablets comply with the test for disintegration of tablets and capsules (*2.9.1*). Use *water R* as the liquid. Add a disc to each tube. Operate the apparatus for 60 min, unless otherwise justified and authorised, and examine the state of the tablets. If any of the tablets has not disintegrated, repeat the test on a further 6 tablets, replacing *water R* with *0.1 M hydrochloric acid*. The tablets comply with the test if all 6 have disintegrated in the acid medium.

Film-coated tablets comply with the disintegration test prescribed above except that the apparatus is operated for 30 min, unless otherwise justified and authorised.

If coated tablets or film-coated tablets fail to comply because of adherence to the discs, repeat the test on a further 6 tablets omitting the discs. The tablets comply with the test if all 6 have disintegrated.

Chewable coated tablets are not required to comply with the test.

Effervescent tablets

DEFINITION

Effervescent tablets are uncoated tablets generally containing acid substances and carbonates or hydrogen carbonates which react rapidly in the presence of water to release carbon dioxide. They are intended to be dissolved or dispersed in water before administration.

TESTS

Disintegration. Place 1 tablet in a beaker containing 200 ml of *water R* at 15-25 °C; numerous bubbles of gas are evolved. When the evolution of gas around the tablet or its fragments ceases the tablet has disintegrated, being either dissolved or dispersed in the water so that no agglomerates of particles remain. Repeat the operation on 5 other tablets. The tablets comply with the test if each of the 6 tablets used disintegrates in the manner prescribed within 5 min, unless otherwise justified and authorised.

Soluble tablets

DEFINITION

Soluble tablets are uncoated or film-coated tablets. They are intended to be dissolved in water before administration. The solution produced may be slightly opalescent due to the added excipients used in the manufacture of the tablets.

TESTS

Disintegration. Soluble tablets disintegrate within 3 min when examined by the test for disintegration of tablets and capsules (*2.9.1*), but using *water R* at 15-25 °C.

Dispersible tablets

DEFINITION

Dispersible tablets are uncoated or film-coated tablets intended to be dispersed in water before administration giving a homogeneous dispersion.

TESTS

Disintegration. Dispersible tablets disintegrate within 3 min when examined by the test for disintegration of tablets and capsules (*2.9.1*), but using *water R* at 15-25 °C.

Fineness of dispersion. Place 2 tablets in 100 ml of *water R* and stir until completely dispersed. A smooth dispersion is produced, which passes through a sieve screen with a nominal mesh aperture of 710 µm.

Orodispersible tablets

DEFINITION

Orodispersible tablets are uncoated tablets intended to be placed in the mouth where they disperse rapidly before being swallowed.

TESTS

Disintegration. Orodispersible tablets disintegrate within 3 min when examined by the test for disintegration of tablets and capsules (*2.9.1*).

Modified-release tablets

DEFINITION

Modified-release tablets are coated or uncoated tablets which contain special excipients or which are prepared by special procedures, or both, designed to modify the rate, the place or the time at which the active substance(s) are released.

Modified-release tablets include prolonged-release tablets, delayed-release tablets and pulsatile-release tablets.

PRODUCTION

A suitable test is carried out to demonstrate the appropriate release of the active substance(s).

Gastro-resistant tablets

DEFINITION

Gastro-resistant tablets are delayed-release tablets that are intended to resist the gastric fluid and to release their active substance(s) in the intestinal fluid. Usually they are prepared from granules or particles already covered with a gastro-resistant coating or in certain cases by covering tablets with a gastro-resistant coating (enteric-coated tablets).

Tablets covered with a gastro-resistant coating conform to the definition of coated tablets.

PRODUCTION

For tablets prepared from granules or particles already covered with a gastro-resistant coating, a suitable test is carried out to demonstrate the appropriate release of the active substance(s).

TESTS

Disintegration. For tablets covered with a gastro-resistant coating carry out the test for disintegration (*2.9.1*) with the following modifications. Use *0.1 M hydrochloric acid* as the liquid. Operate the apparatus for 2 h, or other such time as may be justified and authorised, without the discs and examine the state of the tablets. The time of resistance to the acid medium varies according to the formulation of the tablets to be examined. It is typically 2 h to 3 h but even with authorised deviations is not less than 1 h. No tablet shows signs of either disintegration (apart from fragments of coating) or cracks that would allow the escape of the contents. Replace the acid by *phosphate buffer solution pH 6.8 R* and add a disc to each tube. Operate the apparatus for 60 min and examine the state of the tablets. If the tablets fail to comply because of adherence to the discs, repeat the test on a further 6 tablets omitting the discs. The tablets comply with the test if all 6 have disintegrated.

Dissolution. For tablets prepared from granules or particles already covered with a gastro-resistant coating, a suitable test is carried out to demonstrate the appropriate release of the active substance(s), for example the test described in *Dissolution test for solid dosage forms* (*2.9.3*).

Tablets for use in the mouth

DEFINITION

Tablets for use in the mouth are usually uncoated tablets. They are formulated to effect a slow release and local action of the active substance(s) or the release and absorption of the active substance or substances at a defined part of the mouth. They comply with the requirements of the monograph on *Oromucosal preparations (1807)*.

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TAMPONS, MEDICATED

Tamponae medicatae

Additional requirements for medicated tampons may be found, where appropriate, in other general monographs, for example Rectal preparations (1145), Vaginal preparations (1164) and Ear preparations (0652).

DEFINITION

Medicated tampons are solid, single-dose preparations intended to be inserted into the body cavities for a limited period of time. They consist of a suitable material such as cellulose, collagen or silicone impregnated with one or more active substances.

PRODUCTION

In the manufacture, packaging, storage and distribution of medicated tampons, suitable means are taken to ensure their microbial quality; recommendations on this aspect are provided in the text on *Microbiological quality of pharmaceutical preparations* (*5.1.4*).

LABELLING

The label states the quantity of active substance(s) per tampon.